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An approach for detecting the severity levels of COVID-19 and associated features in district Gujranwala, Pakistan

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Abstract

COVID-19, a pandemic, attacked millions of people's health and economies across the world, particularly in low-income developing countries such as Pakistan. The study aims to develop a novel method and approach to diagnose COVID-19. Clinical features C-reactive protein, ferritin, and D-dimer levels were accessed to check the severity of COVID-19 positive patients. 160 patients were included in this study who had positive signs for COVID-19. Sandwich immune-detection and real time-PCR analyses were performed to access the clinical features of COVID-19. The results of clinical features and real time-PCR assay were compared using Artificial Intelligence (AI). Four classifiers; Support vector machine, Random Forest, K- nearest neighbor, and Neural network, were used to predict the results and the accuracy from these algorithms was 78.6%, 75.4%, 75.4%, and 63.9% respectively. The higher accuracy was from the Support vector Machine which shows 78.6% accuracy of clinical features results obtained from COVID-19 positive patients. In conclusion, this study provides an alternative diagnostic method for COVID-19 patients. Additionally, this study not only provided the diagnostic method but also evaluate severity of clinical features and also the cost-effective diagnosis of COVID-19 detection. The alternative way provided by this this study will be very helpful for the diagnosis of COVID-19 through basic test parameters.

Introduction

The COVID-19 pandemic impacted millions of people globally. It affected the public health and economy, particularly in developing nations with low incomes. Three words make up COVID: "CO" stands for corona, "VI" for virus, and "D" for disease [1]. Over 221 million people worldwide died of the disease in 2021 as a result of COVID-19 [2]. The five nations most impacted by the number of coronavirus cases that have been confirmed are the United States, Brazil, India, Russia, and the United Kingdom [1]. In Pakistan, there were 804,939 confirmed cases of COVID-19 in 2021, with 17,329 deaths, reported to the [3].

Punjab is the area most severely affected by COVID-19 as of August 2021; around 400,000 cases have been noted. With over 400,000 recorded cases and over 12,000 deaths in September 2021, Punjab is the COVID-19 region with the greatest severity as of August 2021 [4]. According to [5], severe COVID-19 causes a state of inflammation that enhances the pathological failure of innate host defense mechanisms. This can lead to effects like multiple organ failure and cytokine storms. In any tissue damage process, C-reactive protein (CRP) is a compatible biomarker and acute-stage protein that manifests in the blood within six to ten hours [6]. Ferritin, a type of iron, is one of the markers of inflammation [7]. Protein fragments, known as D-dimers, are the result of the plasmin-mediated cross-linking breakdown of proteins [8].

Consequently, further investigation into scores related to the course of the disease aids in enhancing diagnostic precision and may even reveal the extent of the illness. Clinical diagnosis can be improved by such initiatives, and the need for expensive diagnostic techniques like CT scans and RT-PCR can be decreased [9]. Even though the number of COVID-19 studies has increased recently, there is a dearth of information in Pakistan, especially in Gujranwala, Punjab, about the laboratory aspects of COVID-19 cases [10]. The study assessed the features of CRP, ferritin, and D-dimer that are linked to COVID-19 [11].

A subfield of science and engineering known as artificial intelligence (AI) deals with the computational modelling of intelligent thought and the development of documents that demonstrate that behavior. The dataset is classified using a variety of artificially intelligent classifiers according to the outcomes. The available classifiers include Random Forest, SVM, K-nearest neighbor, and neural networks. A random forest is a machine-learning system for classification that is capable of regression and predictions [12].

The Support Vector Machine (SVM) is a boundary and ordering method that applies selection requirements and features [13]. K-nearest neighbor (KNN) is used as a basic prediction engine to complete tasks such as classification after deciding on the right parameters and feature subset [14]. Computational analysis tools called neural networks (NN) are inspired by the nervous system found in nature. They consist of neurons, which are networks of interconnected computer processors that can process and retrieve information in parallel. Their ability to learn from prior instances, evaluate non-linear data, cope with uncertain data, and generalize the model so that it can be utilized with new data has made them a particularly acceptable analytical tool [15]. The infectious disease COVID-19 has some FDA approved antiviral drugs that are, nirmatrelvir-ritonavir (Paxlovid), remdesivir (Veklury) or molnupiravir (Lagevrio). These drugs also have many side effects [16]. In the Gujranwala region of Pakistan, the study helped to evaluate the severity of the disease in COVID-19 positive cases. It involved comparing the ferritin level, D-dimer, and CRP levels of COVID-19 patients with RT-PCR results to diagnose COVID-19. The study aided in offering COVID-19 patients a different diagnostic strategy. This study offered a cost-effective diagnosis of COVID-19 in addition to the severity of its clinical features.

Materials and methods

Inclusion and exclusion criteria

We have selected a sample size of 272 patients in the study based on symptoms, i.e., fever, coughing, and sore throat. The patients had low oxygen levels or breathing rates of over 30 cycles per minute. Out of total 272 patients, 160 didn't have any past medical records. The total number of people studied was 160, having median age of 49 years and range of 30-70 years. There were 96 (60%) males, in which young males are 74 and 64 (40%) females, in which young females are 32 in the group. Gender and age disparities between the two groups found to be significant.

Patients with incomplete health records or a history of Type 2 diabetes, failure of the liver, kidney failure, or an active tumor were not allowed to take part in the

study.

Blood samples were collected from the Phlebotomy Department, Razia Shafi Critical and Medical Care Hospital, Kamoke, Gujranwala, Pakistan. The Institutional Ethical Review Board, of University of Sialkot approved the study at the University of Sialkot. For CRP analysis, blood samples were collected in serum tubes with or without clot activators [17]. For D-dimer analysis, blood samples were mixed with sodium citrate in silicon tubes. For ferritin analysis, venous blood samples were drawn into serum tubes with gel or a clot activator [18].

C-Reactive protein test

The serum was collected by centrifugation of blood samples at 2500 rpm for 10 min. 1.8 mL of the collected serum was stored immediately at -20 °C in a 2 mL cryovial, leaving 0.2 mL for expansion [19]. The ichroma™III CRP test kit method (Sant'Antonio Abate (NA), Italy) was used to detect CRP levels in blood samples to detecting luminescent antibodies. The antibodies bind to CRP antigens, forming complexes trapped on the test matrix. The fluorescence intensity was converted into a CRP concentration using calibration (**Fig. 1**). Test results were given in ng/mL, with a typical range of 2.5-10 ng/mL. Levels above 10 ng/mL indicate illness [20].

D-Dimer test

The plasma of the blood samples was collected from the whole blood. The samples were processed for plasma extraction within 3 hrs of sampling as the storage of the samples may affect the D-Dimer test outcomes [21]. 10 µL of sample was transferred (human whole blood, plasma) to a tube containing the detection buffer and the mixture was shaken 10 times to mix completely. 75 µL of the sample mixture was added into the cartridge's sample well and the sample-loaded cartridge was placed at room temperature (RT). A sandwich immune-detection method used a buffered detection system for antibodies to bind to antigens and produce complexes of antibodies that migrate into the nitrocellulose matrix. The other immobile antibodies on the test strip were able to retrieve the antigen as well as antibody complexes from this matrix (**Fig. 2**). The instrument for the ichroma™III test was used to measure D-dimer levels in the sample based on the number of antigen and antibody complexes that form and the quantity of antigen present in the sample which results in more signal luminescence on the antibody detector [22]. D-dimer levels usually vary from 50 to 500 ng/mL. D-dimer levels in diseased patients ranges from 500 ng/mL to 10,000 ng/mL.

Ferritin test procedure

The analysis of protein serum Ferritin levels in the blood was performed following the given protocol [23]. 5mL of blood was required for each chemical and hormonal study. The samples were left at the ambient temperature for 60 min. The samples were then centrifuged for 15 min at 2500 rpm to obtain the serum, which was subsequently stored at -20° C [24]. The ichroma™III system was used to detect luminescent antibodies in the sample. The test strip extracted the fluorescence-labeled antigen-antibody complex. The ferritin concentration can be determined based on the signal strength. A control protein was used for as a control. Ferritin levels typically range from 50 to 250 ng/mL, but in infected patients, it can be higher than 250 ng/mL, even exceeding 1000 ng/mL [23].

Comparison of the severity of clinical features with COVID-19 RT-PCR

The key test for COVID-19 detection was RT-PCR for viral mRNA from nasopharyngeal swab. It was used by government centers according to with WHO guidelines for COVID-19 analysis. The laboratory records containing ferritin, D-dimer, and CRP were obtained for study participants.

Statistical analysis

The set of data derived from test results was analyzed based on different artificial intelligence (AI) methods including random forest, SVM, K-nearest neighbor, and artificial neural network computations.

Results and Discussion

Subject Dataset

The total number of 272 participants, out of which 112 were excluded. The reason to exclude the subject had missing data records. The demographic characteristics of the study participants are presented in **Table 1.** Overall, 160 participants were involved in the study, with a range of ages between 30 and 70 years and a median age of 49. There were 64 (40%) females and 96 (60%) males. 52 (32.5%) of the COVID-19

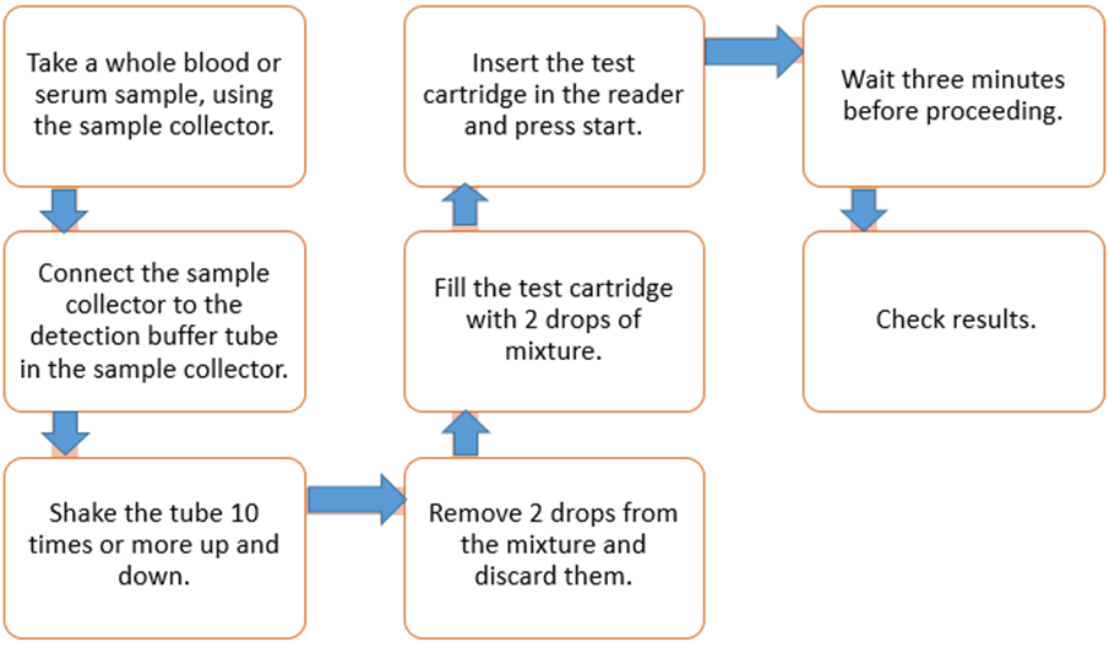

Fig. 1: Flow chart for the whole procedure of analysis for the levels of C- Reactive protein in serum or plasma sample.

negative outcomes of RT (Group 1) and 108 (67.5%) of the COVID-19 positive results (Group 2) were included. Age and gender differences were statistically significant in two groups. **Table 1** displays the results of biochemical parameters obtained from blood samples. The results of biochemical parameters from blood samples indicated that out of 160 patients with SARS-CoV2 disease, the percentage of COVID-19 disease was higher in men (60%) than in women (40%) (**Table 2**).

Clinical Parameters

A total of 64 Males and 44 females were positive COVID-19 RT-PCR reports. the routine laboratory data examined for special chemistry of the COVID-19 patients admitted to the hospital between March 1, 2021, and August 1, 2021. Among these patients 56% of patients had high ferritin levels, 79% had elevated CRP levels, and 80% had elevated D-dimer levels (**Table 3**).

Young males and females as typical examples to demonstrate the laboratory markers trend analysis in case of COVID-19 were analyzed. This analysis aimed to clarify the role of basic laboratory parameters in disease detection (severe infection). This choice is meant to show how COVID-19 infection manifests in adult males and females with diverse age-related multisystem inflammatory syndromes. To build a smooth trending graph and observe the fluctuations in the parameters throughout COVID-19 diagnoses, the daily laboratory results of the patients were employed in this assessment.

CRP, Ferritin and D-dimer in females

In the trending graphical representation of CRP in females the value varies from 2.5 mg/L to 300 mg/L. The ranging values of elevated CRP are shown in blue lines, which indicates the rising level of CRP in patients (**Fig. 3A**). The serum Ferritin in females vary from 50 ng/mL to 1000 ng/mL (**Fig. 3B**). The trending graph of D-dimer in females the value varies from 50 ng/mL to 10,000ng/mL. The positive value is ranging from 500ng/mL to 10,000ng/mL that show above the orange line. The ranging values of elevated D-dimer are show in blue lines, which showed the increasing level of D-dimer in patients (**Fig. 3C**).

CRP Ferritin and D-dimer in males

The values of elevated CRP are shown in blue lines, which indicate the rising level of CRP in male patients (**Fig. 4A**). Resulted indicated that in contrast to females, samples from male patients showed the highest value of CRP. The possible reason of raising values in males might be the higher exposure of males to other peoples in Pakistan rather than females. The

Table 1: Results of C-reactive protein, D-dimer, and Ferritin performed in Razia Shafi pathology lab and their RTPCR COVID-19 reports from public labs. Only 30 patient reports are shown here.

Sample	Gender	CRP	D-dimer	Ferritin	RT PCR Covid	Binary form
Normal value		2.5-10 mg/L	50-500 ng/mL	50-250 ng/mL	Negative	
effected values		10-300 mg/L	500-10000 ng/mL	250-1000 ng/mL	Positive	
P1	Male	98.13	1170.8	350	positive	1
P2	Male	231.6	837.1	267	positive	1
P3	Male	15.2	579.7	253	positive	1
P4	Male	100.7	862	242	positive	1
P5	Male	2.9	275	198.19	negative	0
P6	Male	19.2	542	44.8	negative	0
P7	Male	18.2	132.1	458.4	negative	0
P8	Male	159.8	122.15	433.5	positive	1
P9	Female	10.2	118.02	205.8	positive	1
P10	Male	102.52	2205.86	678.5	positive	1
P11	Male	172.49	225.06	572.4	positive	1
P12	Male	77.9	272.14	222.8	positive	1
P13	Female	9.85	4203.7	243.3	positive	1
P14	Male	16.1	9301.52	438.6	positive	1
P15	Male	73.56	575.1	287.5	positive	1
P16	Female	267.5	189.5	220.3	negative	0
P17	Male	40.6	846.5	687.8	positive	1
P18	Male	258.7	172.1	122.7	negative	0
P19	Female	123.28	5536.23	619.2	positive	1
P20	Female	34.54	240.3	204.76	negative	0
P21	Female	50.7	1676.6	436	positive	1
P22	Male	26.9	221.7	143	negative	0
P23	Male	75.7	346.5	215.8	negative	0
P24	Male	34.1	266.6	350.6	positive	1
P25	Female	64.9	419	237.2	negative	0
P26	Female	19.69	443.3	215.6	negative	0
P27	Male	51.53	1759.21	751.9	positive	1
P28	Female	300.0	420.06	235.1	positive	1
P29	Male	2.50	283.3	267.6	negative	0
P30	Male	12.19	340.3	323.11	negative	0

infection was severe in males as compared to the female patients. The values of serum Ferritin in male patients were between 50 ng/mL to 1000ng/mL. Higher values of Ferritin were investigated in male patients than females indicating the high risk of severe infection in males (**Fig. 4B**). In contrast, the values of D-dimer in males are almost similar when compared to female patients (**Fig. 4C**).

Algorithm accuracy identification

The results obtained by biochemical features were analyzed using Artificial Intelligence Algorithms. The study was conducted to determine the ideal train and test ratio, results showed the accuracy of clinical parameters raising value with COVID-19. Four different algorithms of Artificial intelligence were used. By comparing the accuracy results of all algorithms, it was determined which result accuracy showed the percentile accuracy of our clinical features raising levels with COVID-19. As shown in **Table 4**, we evaluated the dataset percentages, and trial yielded a distinct set of accuracy with the four algorithms Random Forest, SVM, K-nearest neighbor, and artificial neural network. By dividing the data into 62.5% training and 37.5% testing, we received the following results.

Table 2: Characteristics of study subjects

No. of analyzed participants	160
Median age (range)	49 (30-70)
Gender	
No. of males (%)	96 (60%)
No. of females (%)	64 (40%)
No. of COVID-19 -ve patients (%)	52 (32.5%)
No. of COVID-19 +ve patients (%)	108(67.5%)

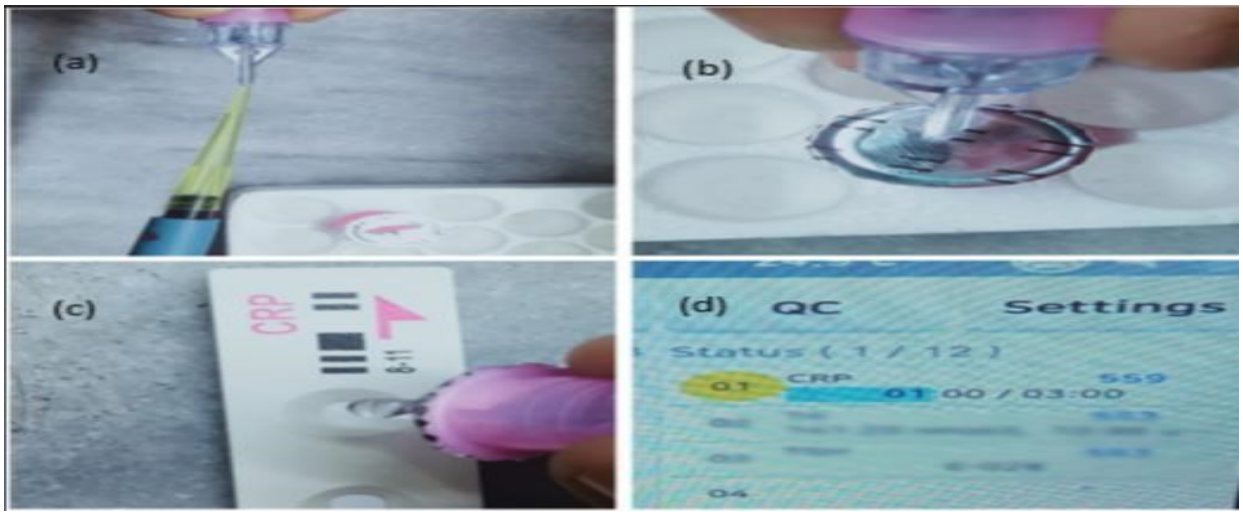

Fig. 2: (a) Loading of 10 µL sample into the collector (b) mixing in detection buffer (c) addition of two drops on cartridge (d) analysis by getting the reading.

The first method Random Forest was tested, which had a 75.4% accuracy by splitting the data into 72.5% for training and 37.5% for testing. The second method used was SVM, which had an accuracy of 78.6% by separating the data into the same percentile for training and testing. The third method used was K-Nearest Neighbor, which had a 75.4% accuracy by separating the data into the same percentile for training and testing. The fourth approach was Neural Network, which had a 63.9% accuracy by separating the data into the same percentile for training and testing.

The data was divided into different groups of classes, and then each class was divided into the percentages as used for all class of the data. In the last, SVM proved to be the most accurate algorithm for categorizing the data-set, outperforming the other classifiers. After the results of Artificial intelligence methods, SVM identified with 78.6% accuracy that COVID-19 positive participants had pointedly higher levels of CRP, ferritin, and D-dimer when compared to COVID-19 negative subjects. The results showed the accuracy of clinical parameters raising value with COVID-19.

According to another studies, which used K- Nearest Neighbor SVM AND Artificial Neural Networks on different blood parameters WBC, CRP, IL-6, procalcitonin, ferritin, LDH, AST, ALT, D-dimer, troponin, lymphocyte and platelet levels are associated with the severity of COVID-19. By using these three classified algorithms they showed an accuracy of 97.86% in his research which is greater than our results [25]. Another research of Antonio

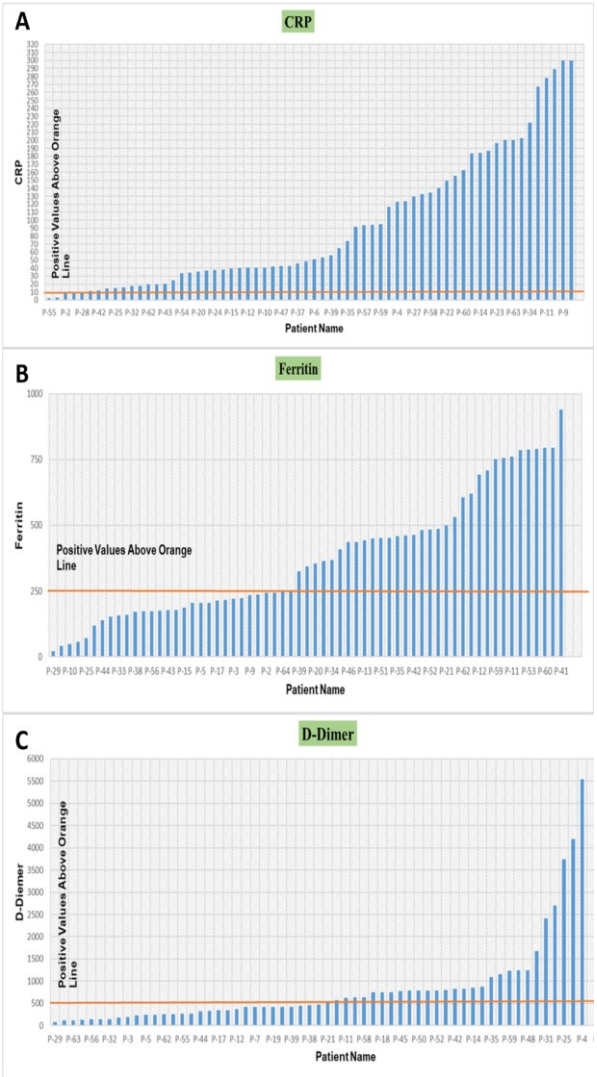

Fig. 3: Trend analysis of (A) CRP, (B) Ferritin, (C) D-dimer in females.

Ramón used k-nearest neighbors (KNN) and support vector machine (SVM) method on C-reactive protein, procalcitonin, glutamyl oxaloacetic transaminase, glutamyl pyruvic transaminase, neutrophils, D-dimer, creatinine, lactic acid and ferritin blood parameters and demonstrated results of best accuracy (92 %) in this research which is also higher than our results [26]. Other manifestation studies reported Random Forest, K- Nearest Neighbor, and Support Vector machine algorithms on different blood parameters i.e., procalcitonin, C-creative protein, lactate dehydrogenase, D-dimer, and lymphocytes. Using these algorithms Random Forest, SVM, and Neural Networks showed 89%, 87.8%, and 84.4% accuracy, respectively. Random forest shows higher accuracy 89% which is greater than our results [27].

According to the severity of the disease presentation, the continuing COVID-19 pandemic is defined by respiratory illness and other systemic clinical features, which are in turn indicated by common laboratory abnormalities. The most significant laboratory alterations include a variety of elevated inflammatory biomarkers, coagulation markers, tissue-specific tissue injury indicators (liver, kidney, cardiac), and abnormalities in the total blood parameters. Depending on the disease's severity, the host's inflammatory reaction to the virus may result in a cytokine storm that can harm multiple organs. Patients with the critical stage of COVID-19 also had severe abnormalities in coagulation measurements, liver and renal function, cardiac and muscular damage biomarkers, and inflammatory biomarkers. D-dimer, ferritin, and CRP are markers for the severe stages of the disease. Biochemistry and immunoassay measures like CRP, D-dimer, and serum Ferritin should be closely monitored in hospitalized patients as signals for potential advancement to the critical stage of disease and death [28].

C-reactive protein is another acute phase reactant produced in response to infection or inflammation (CRP). It is the liver that produces CRP. Since acute inflammation is accompanied by a sharp rise in serum concentration, CRP is now considered to be a more significant indicator of viremia and sepsis. Additionally, CRP participates in the proinflammatory cycle by activating inflammatory cytokines. Ferritin levels that are high contribute to pro-inflammation. A significant acute phase reactant is ferritin, which the body produces when it is inflamed. Infections, as well as hematologic, neoplastic, and rheumatologic disorders, are among these inflammatory conditions [29]. As a defense mechanism, ferritin seeks to decrease the iron supply,

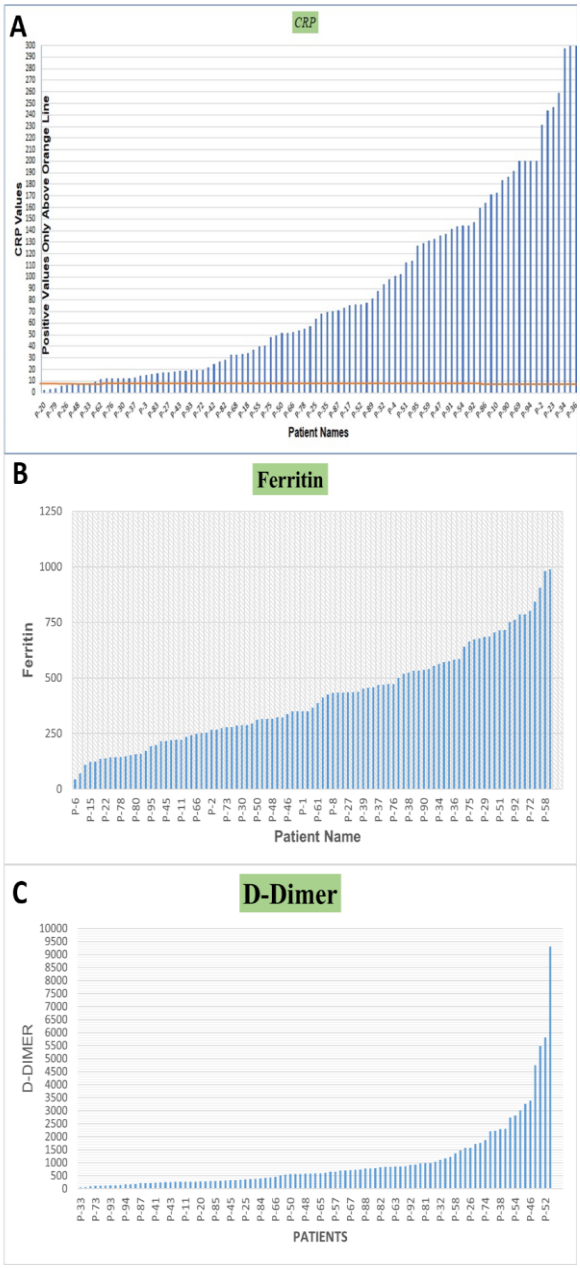

Fig. 4: Trend analysis of (A) CRP, (B) Ferritin, (C) D-dimer in males.

as a result, higher levels of ferritin are seen in cases of high pathogenic loads. Ferritin tends to control the synthesis and release of cytokines, which are responsible for cytokine proinflammatory storms, in addition to reducing the availability of iron. D-dimer, which is the main enzymatic byproduct of cross-linked fibrin by plasmin, is another marker that exhibits an increase in COVID-19 patients. Studies have revealed that rising D-dimer levels are associated with an increased chance of the patient developing septic shock and sepsis. Consequently, routine blood

Table 3: Percentage of patients showing abnormal parameters considered in the study population.

Clinical Parameters	%age of Abnormal results	Elevated	Normal values
CRP	79%	↑	2.5-10 mg/L
D-dimer	80%	↑	50-500 ng/mL
Ferritin	56%	↑	50-250 ng/mL

Table 4: Training and testing data set and accuracy of all algorithms

Training (%): Testing (%)	Random Forest	SVM	K-Nearest Neighbor	Neural Network
62.5% : 37.5%	75.4%	78.6%	75.4%	63.9%

biomarker tests in the laboratory department are a possible COVID-19 diagnostic tool [30].

The study's trend analysis of the numerous biomarkers in COVID-19 patients will aid in understanding the COVID-19 treatment plan as it attempts to contain the cytokine storm in ARDS. Despite numerous current investigations, the pathogenicity of the Novel Coronavirus is still not fully understood, so routine laboratory testing may be helpful in symptom-based treatment plans until the situation is resolved. The results obtained by biochemical features are analyzed using some Artificial Intelligence algorithms. These algorithms are Random Forest, SVM, K-nearest neighbor and Artificial neural network [31].

The first method Random Forest was tested, which had a 75.4% accuracy by splitting the data into 72.5% for training and 37.5% for testing. The second method used was SVM, which had an accuracy of 78.6% by separating the data into the same percentile for training and testing. The third method used was K-Nearest Neighbor, which had a 75.4% accuracy by separating the data into the same percentile for training and testing. The fourth approach was Neural Network, which had a 63.9% accuracy by separating the data into the same percentile for training and testing.

After the results of Artificial intelligence methods, SVM identified 78.6% accuracy that COVID-19 positive participants had pointedly higher levels of CRP, ferritin, and D-dimer when compared to COVID-19 negative subjects. The information used in the study demonstrated the value of common laboratory biomarkers in coronavirus disease 2019 (COVID-19) and will contribute to a better understanding of the condition.

Conclusion

In conclusion, our findings are useful to analyze the COVID-19 disease with routine biochemical tests performed in labs. There is a significant relationship between specific abnormal blood parameters and illness severity status in COVID-19 patients who are hospitalized or not. Use these biochemical features for future disease diagnosis, to improve accuracy and build more reliable diagnosis. In addition, it intends to classify the results using deep learning techniques, which helps to diagnose the condition more professionally and, in less time, to produce better results than other methods. It is possible to down the fear of patients and improve diagnosis to utilize these biochemical features rather than RT PCR. In future, this study can be helpful for the diagnosis of COVID-19 through basic cost-effective parameters in low-income countries.

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Conflict of interest

The authors declare no conflict of interest.

References

[1] Yesudhas D, Srivastava A, Gromiha MM. COVID-19 outbreak: history, mechanism, transmission, structural studies and therapeutics. Infection. 2021;49:199-213.

[2] Bottino F, Tagliente E, Pasquini L, Napoli AD, Lucignani M, Figà-Talamanca L, et al. COVID mortality prediction with machine learning methods: a systematic review and critical appraisal. Journal of personalized medicine. 2021;11:893.

[3] Imran M, Khan S, Khan S, Uddin A, Khan MS, Ambade P. COVID-19 situation in Pakistan: A broad overview. Respirology (Carlton, Vic). 2021;26:891.

[4] Saeed U, Sherdil K, Ashraf U, Younas I, Butt H, Ahmad S. Identification of potential lockdown areas during COVID-19 transmission in Punjab, Pakistan. Public health. 2021;190:42-51.

[5] Potempa LA, Rajab IM, Hart PC, Bordon J, Fernandez-Botran R. Insights into the use of C-reactive protein as a diagnostic index of disease severity in COVID-19 infections. The American journal of tropical medicine and hygiene. 2020;103:561.

[6] Black S, Kushner I, Samols D. C-reactive protein. Journal of Biological Chemistry. 2004;279:48487-90.
[7] Mackay AD, Marchant ED, Munk DJ, Watt RK, Hansen JM, Thomson DM, et al. Multitissue analysis of exercise and metformin on doxorubicin-induced iron dysregulation. American Journal of Physiology-Endocrinology and Metabolism. 2019;316:E922-E30.
[8] Thachil J, Lippi G, Favaloro EJ. D-dimer testing: laboratory aspects and current issues. Hemostasis and Thrombosis: Methods and Protocols. 2017:91-104.
[9] Ikewaki N, Kurosawa G, Iwasaki M, Preethy S, Dedeepiya VD, Vaddi S, et al. Hepatoprotective effects of Aureobasidium pullulans derived Beta 1, 3-1, 6 biological response modifier glucans in a STAM-animal model of non-alcoholic steatohepatitis. bioRxiv. 2021:2021.07. 08.451700.
[10] Raza SQ, Waqar M, Ahmad S, Iqbal H, Saifullah A. Trends Toward Self-Medication Practices During Covid-19 In Gujranwala District: Trends Toward Self-Medication Practices During Covid-19. Pakistan Journal of Health Sciences. 2022:198-202.
[11] Kaftan AN, Hussain MK, Algenabi AA, Naser FH, Enaya MA. Predictive Value of C–reactive Protein, Lactate Dehydrogenase, Ferritin and D-dimer Levels in Diagnosing COVID-19 Patients: a Retrospective Study. Acta Informatica Medica. 2021;29:45.
[12] Breiman L. Random forests. Machine learning. 2001;45:5-32.
[13] Huang M-W, Chen C-W, Lin W-C, Ke S-W, Tsai C-F. SVM and SVM ensembles in breast cancer prediction. PloS one. 2017;12:e0161501.
[14] Guo G, Wang H, Bell D, Bi Y, Greer K. KNN model-based approach in classification. On The Move to Meaningful Internet Systems 2003: CoopIS, DOA, and ODBASE: OTM Confederated International Conferences, CoopIS, DOA, and ODBASE 2003, Catania, Sicily, Italy, November 3-7, 2003 Proceedings: Springer; 2003. p. 986-96.
[15] Holmes J, Sacchi L, Bellazzi R. Artificial intelligence in medicine. Ann R Coll Surg Engl. 2004;86:334-8.
[16] Aboul-Fotouh S, Mahmoud AN, Elnahas EM, Habib MZ, Abdelraouf SM. What are the current anti-COVID-19 drugs? From traditional to smart molecular mechanisms. Virology Journal. 2023;20:241.
[17] Doumatey AP, Zhou J, Adeyemo A, Rotimi C. High sensitivity C-reactive protein (Hs-CRP) remains highly stable in long-term archived human serum. Clinical biochemistry. 2014;47:315-8.
[18] Shattnawi KK, Alomari MA, Al-Sheyab N, Bani Salameh A. The relationship between plasma ferritin levels and body mass index among adolescents. Scientific reports. 2018;8:15307.
[19] Sugden K, Danese A, Shalev I, Williams BS, Caspi A. Blood substrate collection and handling procedures under pseudo-field conditions: evaluation of suitability for inflammatory biomarker measurement. Biodemography and social biology. 2015;61:273-84.
[20] Oh SW, Moon JD, Park SY, Jang HJ, Kim JH, Nahm KB, et al. Evaluation of fluorescence hs-CRP immunoassay for point-of-care testing. Clinica chimica acta. 2005;356:172-7.
[21] Kim TK, Oh SW, Mok YJ, Choi EY. Fluorescence Immunoassay of Human D-dimer in Whole Blood. Journal of Clinical Laboratory Analysis. 2014;28:294-300.
[22] Riley RS, Gilbert AR, Dalton JB, Pai S, McPherson RA. Widely used types and clinical applications of D-dimer assay. Laboratory medicine. 2016;47:90-102.
[23] Bolodeoku J, Coker O, Bains S, Kim T, Anyaeche C. The Performance of the Point of Care Test (POCT) i-CHROMA Ferritin Method and other Methods Enrolled in the RIQAS. J Biochem Analyt Stud. 2020;4.
[24] Yenzeel JH. The Variation in Levels of Some Male Pituitary and Gonadal Hormones in Beta-Thalassemia Major Patients in Iraq. Iraqi Journal of Science. 2017:216-21.
[25] Kalaycı M, Ayyıldız H, Tuncer SA, Bozdag PG, Karlidag GE. Can laboratory parameters be an alternative to CT and RT-PCR in the diagnosis of COVID-19? A machine learning approach. International journal of imaging systems and technology. 2022;32:435-43.
[26] Ramón A, Zaragozá M, Torres AM, Cascón J, Blasco P, Milara J, et al. Application of Machine Learning in Hospitalized Patients with Severe COVID-19 Treated with Tocilizumab. Journal of Clinical Medicine. 2022;11:4729.
[27] Hou W, Zhao Z, Chen A, Li H, Duong TQ. Machining learning predicts the need for escalated care and mortality in COVID-19 patients from clinical variables. International journal of medical sciences. 2021;18:1739.
[28] Das B, Bhatia SY, Pal PM. Evaluation of the role of routine laboratory biomarkers in COVID-19 patients: perspective from a tertiary care hospital in India. Indian Journal of Clinical Biochemistry. 2021;36:473-84.
[29] Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Frontiers in immunology. 2018;9:342848.
[30] Nehring S, Goyal A, Patel B. C Reactive Protein. 2022 Jul 18. StatPearls [Internet] Treasure Island (FL): StatPearls Publishing. 2023.
[31] Boateng EY, Otoo J, Abaye DA. Basic tenets of classification algorithms K-nearest-neighbor, support vector machine, random forest and neural network: a review. Journal of Data Analysis and Information Processing. 2020;8:341-57.